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In silico study of some tetra- and penta-coordinated gold(III) complexes as potential inhibitors of SARS-CoV-2 main protease

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Abstract

During the last 20 years, much interest has been focused on some gold(III) complexes, due to their stability under physiological-like conditions. Gold(III) complexes have a significant effect on enzyme inhibition due to their strong sulfur binding affinity towards various sulfur-containing enzymes such as thioredoxin reductase, glutathione reductase, and cysteine protease. With the advent of SARS-CoV-2 viral infection, there has been a need to find inhibitors that will prevent the virus from acting. Recent research has shown that compounds that have certain functional groups in their structure are effective in inhibiting the main protease of this virus. In this paper, the inhibitor efficiency of the gold(III) complexes ($[Au(DPP)Cl_2]^+$ (**C1**) and $[Au(DMP)Cl_3]$ (**C2**), where DPP=4,7-diphenyl-1,10-phenanthroline and DMP=2,9-dimethyl-1,10-phenanthroline), as well as FDA approved drugs, cinanserin and chloroquine towards the main protease of SARS-CoV2 (M^{pro}) was estimated using the molecular docking simulations. The binding affinity of investigated compounds was examined by the AutoDock 4.2 software. The ligands were prepared for docking by optimization of their geometries by density functional theory (DFT) employing M06-2X functional in combination with the 6-311G(d,p) basis set for C, N, S, Cl, and H, and LAN2DZ basis set for Au. The native bound ligand (N3) was extracted from M^{pro} and binding pocket analysis was performed by the AutoGridFR program. Re-docking was performed with the investigated compounds to generate the same docking pose as found in the co-crystallized form of M^{pro}. Analysis by AGFR showed that the investigated compounds bind in the active site of M^{pro}. The obtained results indicate that the square-planar **C1** shows better inhibitory activity compared to cinanserin and chloroquine. The binding free energy of **C1** is significantly higher than that for FDA drugs, with values of -38.4, -31.8, and -31.2 kJ mol^{-1}, respectively. The obtained results revealed that **C1** and **C2** bind at the same binding pockets to M^{pro} as well as FDA drugs by weak non-covalent interactions. The most prominent interactions are hydrogen bonds, alkyl-π, and π-π interactions. The preliminary results suggest that gold(III) complexes showed good binding affinity against M^{pro}, as evident from the free binding energy (ΔG_{bind} in kJ/mol).

Keywords:

gold(III) complexes, DFT, molecular docking, SARS-CoV2

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Introduction

Gold(III) complexes have a very strong effect on enzyme inhibition due to their strong sulfur binding affinity towards various sulfur-containing enzymes such as thioredoxin reductase, glutathione reductase, and cysteine protease. With the advent of SARS-CoV-2 viral infection, there has been a need to find inhibitors that will prevent the virus from acting. Recent research has shown that compounds that have certain functional groups in their structure are effective in inhibiting the main protease of this virus.

Methodology

In this paper, the inhibitor efficiency of the gold(III) complexes ($[Au(DPP)Cl_2]^+$ (**C1**) and $[Au(DMP)Cl_3]$ (**C2**), where DPP=4,7-diphenyl-1,10-phenanthroline and DMP=2,9-dimethyl-1,10-phenanthroline), as well as FDA approved drugs, cinanserin and chloroquine towards the main protease of SARS-CoV2 (M^{pro}) was estimated using the molecular docking simulations. The binding affinity of investigated compounds was examined by the AutoDock 4.2 software. The ligands were prepared for docking by optimization of their geometries by density functional theory (DFT) employing M06-2X functional in combination with the 6-311++G(d,p) basis set for C, N, S, Cl, and H, and LAN2DZ basis set for Au.

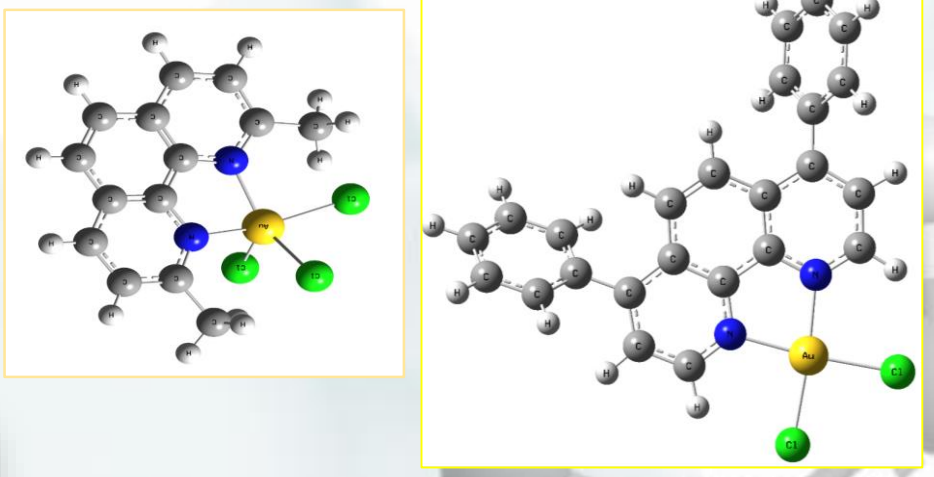

Figure. 1.The structure of studied gold(III) complexes C1 (left) and C2 (rignt)

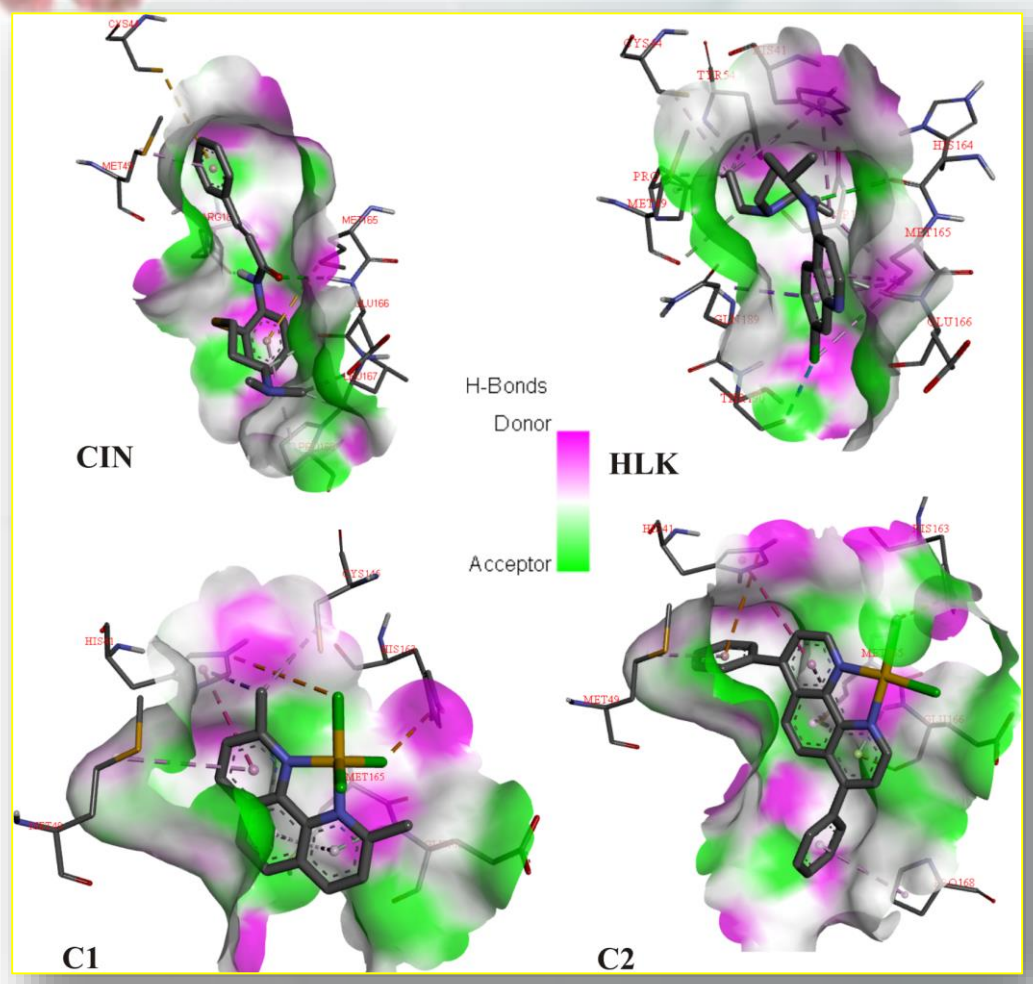

Figure. 2. 3D diagrams of noncovalent interactions between proteins and complexes

	ΔG_{bind} (kcal mol^{-1})	K_i (nM)
C1	-9.18	0.18
C2	-6.13	32.09
CIN	-7.60	2.70
HLK	-7.20	5.26

Table 1.Thermodynamic data obtained by docking simulation of tested compounds with SARS-CoV-2 M^{pro}

Results

Docking was performed with the investigated compounds to generate the same docking pose as found in the co-crystallized form of M^{pro}. Analysis by AGFR showed that the investigated compounds bind in the active site of M^{pro}. The obtained results indicate that the square-planar **C1** shows better inhibitory activity compared to cinanserin and chloroquine. The binding free energy of **C1** is significantly lower than that for FDA approved drugs, with values of -9.18, -7.60, and -7.20 kcal mol^{-1}, respectively.

Conclusion

- Complexes **C1** and **C2** bind at the same binding pockets to M^{pro} as well as FDA drugs by weak non-covalent interactions.
- The most prominent interactions are hydrogen bonds, alkyl-π, and π-π interactions.
- The preliminary results suggest that gold(III) complexes showed good binding affinity against M^{pro}, as evident from the free binding energy (ΔG_{bind} in kcal/mol).

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